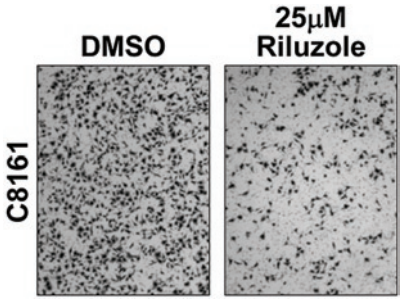
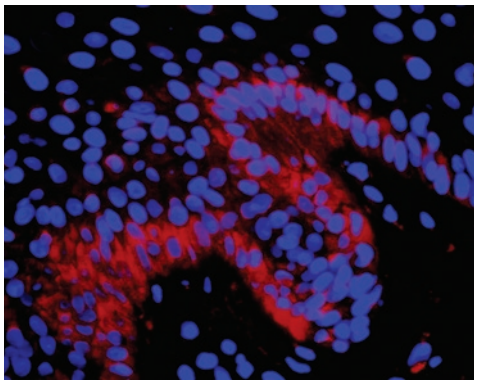
Role of Riluzole



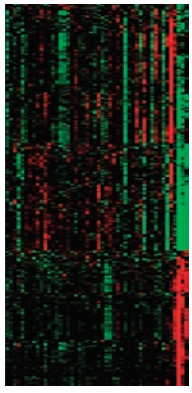
The majority of human melanomas ectopically express the metabotropic glutamate receptor-1 (GRM1), and inhibition of this receptor with riluzole has proved useful in blockade of mitogen-activated protein kinase and phosphatidylinositol-3-kinase/AKT signaling and involution of tumors in patients. Le and colleagues discovered that treatment of human melanoma cell lines with the glutamate release inhibitor riluzole or the specific GRM1 agonist BAY 36-7620 attenuated melanoma cell transformation via a decrease in migration, invasion, and proliferation of these cells, suggesting that these effects likely occur through blockade of GRM1 signaling. These mechanistic results pave the way for the development of riluzole-based combination therapies. ***See page 2240***

Persistently Activated Epidermis



Complex interactions among immune cells, endothelial cells, and fibroblasts contribute to pathogenic fibrotic events in systemic sclerosis (SSc). Aden and colleagues found abnormal activation of the epidermis in SSc. Also, IL-1α, which initiates keratinocyte activation following injury, was increased. Stress signaling via the IL-1α downstream factors MAPK, c-Jun, and p38 was also induced in SSc epidermis. Together, these findings indicate that IL-1α antagonism may offer a therapeutic mechanism to block epithelial–fibroblast interactions to reduce persistent fibroblast activation and subsequent debilitating fibrosis in SSc patients. ***See page 2191***

Differential Irritation



Irritant contact dermatitis (ICD) most often results from repeated exposure to weak irritants. In a genome-wide expression analysis of irritated human epidermis using microarrays representing 47,000 transcripts, Clemmensen and colleagues found that different pathways were activated in the epidermis in response to exposure to nonanoic acid or sodium lauryl sulfate. Analysis of early and late time points revealed that most of the early-response genes were quickly turned off, supporting the notion that the effects of chronic exposure cannot be extrapolated from studies of acute exposure. Furthermore, 23 potential biomarkers common to cumulative skin irritation were identified, and these transcripts offer a starting point for further studies of the mechanisms of ICD. ***See page 2201***

Bacteria for Defense

Previous studies reported that *Staphylococcus epidermidis* on the skin produces antimicrobial peptides to inhibit pathogenic organisms and modulates inflammation through Toll-like receptors (TLRs). Lai and colleagues found that molecules secreted by *S. epidermidis* increased the expression of β-defensins 2 and 3 in murine skin and undifferentiated human keratinocytes, rendering these cells more resistant to certain pathogens via a TLR2-dependent mechanism. Thus, this commensal bacterium induces antimicrobial peptide expression and enables the skin to mount an enhanced immune response. These findings highlight potential pitfalls of using antimicrobial agents indiscriminately to fight infections. ***See page 2211***

Pervasive Heterogeneity

T-cell-receptor monoclonality was previously considered dogma for lymphomas, especially cutaneous T-cell lymphomas such as Sézary syndrome (SS). Using GeneScan analysis to investigate skin and blood samples from SS patients, Fierro and colleagues demonstrated that clonal heterogeneity was more frequent than homogeneity. Importantly, the presence of an oligoclonal pattern in the skin correlated with a longer survival time, and the appearance of new oligoclones during treatment was associated with a stronger response to extracorporeal photochemotherapy, suggesting that detection of heterogeneity will be useful in making prognosis and treatment decisions for SS patients. ***See page 2312***

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